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TITLE THE MODIFICATION OF DAVYDOV SOLITONS BY THE EXTRINSIC H-N-C=O GROUP

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THE MODIFICATION OF DAVYDOV SOLITONS

BY THE EXTRINSIC H-N-C=O GROUP

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INTRODUCTION

The molecular mechanisms which underlie general anesthesia are not clearly understood. This lack of understanding may be attributed to the fact that there are two comparatively separate classes of pharmacologic agents to consider (both intravenous and volatile) which induce general anesthesia. It may also be attributed to the fact that investigators in the field are divided into two differing camps of thought: (1) those who believe that anesthetics work by altering normal membrane fluidity, and (2) those who believe that anesthetics work by perturbing normal protein function. This controversy concerning the fundamental mechanism is clearly not a black and white issue. Nevertheless, there appears to be growing evidence that the "perturbed protein" hypothesis holds greater promise over the "altered fluidity" hypothesis in explaining the molecular mechanisms of general anesthesia.[1] The simplest working idea is that general anesthetics act by binding directly to a particularly sensitive protein, which may or may not be located in a lipid membrane, and inhibiting its normal function.

In this article, the "perturbed protein" hypothesis will be employed in order to postulate a new mechanism of action for intravenous anesthetic agents. In accordance with theory, it will be shown that intravenous agents are capable of changing localized structures within proteins which, in turn, results in an alteration of normal protein dynamics. Volatile agents (such as Halothane and Enflurane) will not be discussed, since this article will concentrate on a specific class of pharmacologic compounds which contain the H-N-C=O (or amide-I) moiety. Barbiturates are the most common intravenous agents in this class and, therefore, they will be the focus

of attention. However, this article will also discuss how several similar classes of agents called hydantoins, succinimides, glutethimides, urethanes and a neurotransmitter called gamma-aminobutyric acid (GABA) are capable of perturbing normal protein function. In addition, this article will conclude with a look at glycoproteins in relation to the H-N-C=O moiety. It will be argued that the same amide-I group, which is found as a major substituent in the sialic acid fraction of glycoproteins, may act as an inherent modulator of glycoprotein behavior. An analogy will be drawn between the perturbing role of an H-N-C=O moiety in an anesthetic agent and an H-N-C=O moiety in the sialic acids of a glycoprotein.

Questions which arise naturally from the "perturbed protein" hypothesis are: 1) what functions of proteins are disturbed by intravenous anesthetic agents, 2) which proteins are disturbed during general anesthesia, and 3) are certain proteins by virtue of their location in a cell more important than others? Some of the answers to these questions are discussed below and many of the points that are introduced below will be given a detailed explanation in subsequent sections.

In relation to question number one, it is constructive to make the ansatz that intravenous anesthetics work by altering both the normal energy organizing and transporting functions within proteins. However, a limitation of such a postulate is that there has been no prominent dynamical model on which to compare ideas against experiment. In other words, the "perturbed protein" hypothesis has had no specific context on which to test its validity. However, this unsatisfying situation may have changed in 1973 when Davydov and Kislukha,[2] proposed a mechanism whereby energy could be transported efficiently along a one-dimensional molecular chain. In a paper entitled "Solitary Excitations in a One-Dimensional Molecular Chain," the authors considered how energy could be transferred via a coupling of intramolecular excitations and intermolecular displacments. The coupling of excitations to displacements, and vice versa, lead to the production of a solitary wave in the one-dimensional molecular chain which did not disperse. During this same year, Davydov[3] published a second paper entitled "The Theory of Contraction of Proteins under their Excitations," where he expanded this solitary wave concept to the alpha-helical protein in the context of muscle contraction. In this second paper it was proposed that myosin, a major component of contractile proteins which has an alpha-helical tail of approximately 900 Å, propagates a soliton which squeezes and pulls on the actin filaments around it. This action serves to slide the actin and myosin filaments together, which results in muscle contraction. Since 1973, Davydov and his co-workers have published a number of papers on solitons in alpha-helical proteins. They address the important property of efficient energy transfer by proteins over distances which are large in terms of biological dimensions. In addition, they have considered the role of electron transport by the soliton mechanism, where the

presence of an extra electron causes a lattice distorsion in the protein which stabilizes its motion.[4] Such an "electrosoliton" is phenomenologically similar to a "neutral soliton," where intramolecular excitatiors (associated with the extra electron) are coupled to intermolecular displacements. Thus it is possible that charge transfer across membranes, transductive coupling across membranes and energy transport along filamentous cytoskeletal proteins may be understood in terms of a soliton mechanism, since these functional classes of proteins are thought to contain structural units with significant alpha-helical character. The soliton model is one of several concepts for protein dynamics which should attract the careful attention of biologists. Clearly, it is not the answer to every dynamical behavior in proteins. Nevertheless, is motivating new questions and experiments in protein dynamics. In this article, the soliton model will be used as a paradigm for understanding the molecular mechanism of general anesthesia. The disturbance of soliton propagation will be related to anesthetic activity.

In relation to question number two, it makes sense to postulate that the dynamical behavior of any protein, regardless of structural configuration, may be perturbed by an intravenous anesthetic. However, for purposes of simplicity, this article will center its discussion on the alpha-helical protein. This emphasis on the alpha-helix is justifiable, since the complication of translational variance within the protein backbone is avoided* and since the helical configuration is the most common of protein structures. Alpha-helical proteins are found in both the membrane and cytoskeletal fractions of cells. It has been estimated that up to one third of membrane proteins are in the helical configuration, based on circular dichroism studies, with the remainder of proteins in a random coil form.[5] Helical membrane proteins usually consist of hydrophobic amino acids and have a length in the range of 30-70 Å (5-10 turns). In the cytoskeleton, the helix is also a common structural motif, where there are at least two important classes of contractile proteins that are highly alpha-helical: tropomyosin and myosin. In addition to the contractile system, the extensive network of intermediate filaments in the cytoskeleton also demonstrates predominant helical character.[6] Cytoskeletal proteins tend to be much longer than membrane proteins (400-1600 Å) and they also tend to form highly stable coiled-coil structures which are capable of polymerizing in a head-to-tail configuration.[7,8] This end to end configuration creates exceptionally long alpha-helical networks within the cytosol.

*In these proceedings, the article by P. S. Lomdahl addresses the more complicated issue of intramolecular excitations coupled to intermolecular displacements in a globular protein. In such translationally variant proteins, the activity of an anesthetic agent would depend more significantly on its location within the three-dimensional protein structure.

Given the appreciation that alpha-helical proteins are predominant membrane and cytoskeletal structures makes it possible to hypothesize a new mechanism of action for hydrogen bonding anesthetic agents. Hypnotic agents which contain the amide-I moiety, such as barbiturates, are capable of perturbing solitons in alpha-helical proteins. This occurs via an alteration of hydrogen bond structure in the alpha-helix that is promoted by the anesthetic agent. This change in hydrogen bond configuration, in turn, modifies the intramolecular excitation and intermolecular vibrational properties of the protein. This perturbation of energy transduction through the helix need not involve a global change in alpha-helical configuration. It need involve merely a modification of structure in one portion of a helix which spans the lipid bilayer or traverses the cytosol of a cell. A simple analogy of this concept is illustrated by an electric circuit. If the flow of electricity in a circuit is modified at one

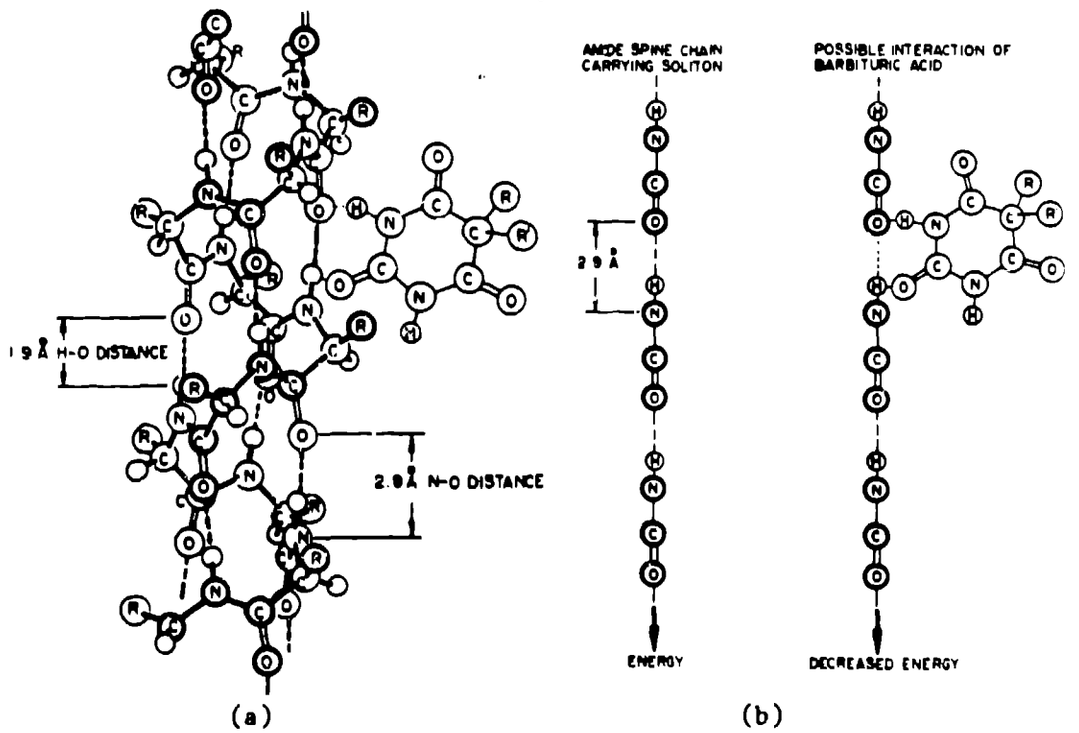

Fig. 1. (a) One of barbiturate's possible interactions with an alpha-helical protein via its H-N-C=O moities. The spiral configuration of the protein is stabilized by its weak hydrogen bonds and the binding of a barbiturate changes the localized structure within the helix.
(b) Isolated view of barbiturate's interaction with the one-dimensional amide-I spine system that supports solitons in the alpha-helix. Such an interaction alters the critical one-dimensional configuration and hydrogen bond relations in the system.

point, then the flow of electricity throughout the entire circuit can be altered. Likewise, in an alpha-helix, if the propagation of a soliton is disrupted by an anesthetic molecule at one bond then the movement of the soliton throughout the rest of the molecule can be altered.

In relation to question number three and following the idea that transductive alpha-helical proteins span the lipid bilayer, this article will emphasize two biological membranes as the principal sites for anesthetic activity: 1) the cellular (neuronal) membrane, and 2) the mitochondrial (inner) membrane. Although there are other sizable membranes within a cell, such as nuclear membrane, endoplasmic reticulum and golgi apparatus, these bilayers are not proposed to be important to the mechanism of general anesthesia. Only membrane proteins that are related directly to intercellular communication and energy production will be considered as the primary targets for anesthetic agents. This assumption does not preclude the possibility that other membrane proteins are inhibited by hydrogen bonding anesthetic agents but these effects will be considered as secondary in the production of unconsciousness.

In addition, it should be mentioned that cytoskeletal proteins may be inhibited by hydrogen bonding anesthetic agents. However, the importance of this effect is rather controversial, since little is known about the energetics of this complex and heterogeneous network of proteins. Clegg[9,10] has speculated that the extensive cytoskeletal framework plays a greater role than simple structural support and cellular motility. He proposes that the cytoskeleton coordinates the energetics of the intracellular soup. The cytoskeleton may provide a matrix on which the so-called soluble enzymes attach and coordinate their energetic activities. Cytoskeletal proteins are known to be associated closely with both the cellular and mitochondrial membranes. Membranes may "talk" to the cytoskeleton and vice versa. Therefore, complete models of general anesthesia should consider the interrelations between these anatomically distinct regions within neurons.

Common to this hypothesis of barbiturate (and related compound) activity is an interference with energetic membrane and cytoskeletal function. The soliton is proposed as an important example of such functions. Although solitons are capable of traversing channels filled with noise, these nonlinear pulses are still susceptible to perturbation. In relation to this fact, Green[11] has categorized biological energy into two broad and encompassing categories: 1) valence vibrational energy, and 2) gradient or ionic potential energy. Given this classification, it should be clear that hydrogen bonding anesthetic agents are capable of interfering with the first suggested category of biological energy. This action may occur at any of the three sites which have been empahsized. At the neuronal membrane, such an action will result in a diminution of communication

between neurons. Decreased axonal conduction, decreased neurotransmitter action and increased release, and decreased synaptic signaling all point to the fact that membranes are less talkative and sensitive to their neighbor's messages.[12] This inhibitory action may involve both the protein and the substantial glycoprotein fractions on the neuronal membrane and in a later section of this article the glycoprotein role, with respect to transductive coupling, will be introduced. At the mitochondrial membrane, such an action will result in a diminution of ATP synthesis. It has been shown experimentally that barbiturates inhibit mitochondrial activity by acting between the iron-sulfur centers of complex I and coenzyme Q.[13] In other words, the anesthetic molecule stops electron transport and oxidative phosphorylation at the very beginning of the ATP synthesis process. This location of activity is consistent with the hypothesis for barbiturate action, since complex I contains the first organization of proteins which are reputed to transport electrons and since a shutdown at complex I will halt the majority of activities of the tripartite repeating unit. At the cytoskeleton, such an action may result in a decreased coordination between the intricate intertwinings of the long and filamentous proteins. Apparently, the shape of the cytoskeleton is dependent on the various micro-environmental concentrations of ATP and Ca^{2+} within the neuron.[6] Barbiturates may interfere with these subtle energy demanding processes and such a loss of coupling from within could alter the cytoskeleton's response to membrane commands. Gradient energy, or the separation of charge across a lipid bilayer, can also be perturbed by hydrogen bonding anesthetic agents. This is understandable because the second suggested category of biological energy is basically a manifestation of valence vibrational energy. The movement of charge across a membrane must first be initiated by an energetic change in the structure of proteins.[14] For example, it is thought that electrons move back and forth across the inner mitochondrial membrane during oxidative phosphorylation. According to the model by Mitchell,[15] this movement of electrons is associated with the concomitant transport of protons and with the establishment of a proton gradient that drives ATP synthesis. Such a hypothesis assumes that the proton has a channel, or an ionophore, through which it can move as it is shunted by the electron transport process and it also assumes that the protein which transports electrons spans the thickness of the inner mitochondrial membrane (~ 50-60 Å). It is plausible that solitons which transport electrons, in conjunction with the other components of the membrane, are a mechanism whereby gradient energy is maintained. The pairing of a proton with the negative charge and the effective mass of an electrosoliton could result in the movement of the proton across the membrane. With this view, general anesthesia can be understood as a loss of both vibrational and gradient energies.

In the brain consciousness can be likened to the "frosting on the metabolic cake." In other words, a relatively small cutback in total metabolic output of the CNS (about 10-15%) will result in

unconsciousness. Therefore, it is necessary that barbiturates inhibit only a select percentage of total alpha-helical protein activities. This will result in a relative loss of communication between neurons which is manifest as a loss of consciousness. In the anesthetic state, the neuronal membranes are quiescent and demanding a smaller energy supply. This is balanced by a decreased synthesis of ATP by mitochondria so that the relative turnover at both membrane sites is diminished. Barbiturates are capable at acting at both sites. This helps to explain the fact that during barbiturate anesthesia the brain settles down to a metabolic valley where demand for an energy supply meets production of the energy source. It also helps to explain the fact that during general anesthesia there is very little change in the apparent energy charge of the neuron. This is exemplified by the fact that concentrations of ATP, ADP, AMP and phosphocreatine in the cytosol remain at preanesthetic concentrations.[16]

SOLITONS: A MECHANISM TO CONSIDER IN BIOENERGETICS

Central to the soliton concept* is the fact that the amide-I resonance (essentially C=O stretch) is intrinsic to every peptide bond of every protein and, therefore, might act as a potential well for the storage and transport of biological energy. However, the amide-I resonance has not been seriously so considered because the line widths of typical amide-I absorption peaks implies a lifetime (due to linear coupling between amide-I groups) on the order of 10^{-12} to 10^{-13} seconds. This period is much too short for normal biological processes. Davydov's concept is that the lifetime of these vibrational excitations can be markedely increased by two coupled fields within the protein: 1) the energy released by ATP hydrolysis introduces a localized amide-I (intramolecular) vibrational excitation that goes on to induce longitudinal sound waves on the alpha-helix, and 2) the induced longitudinal sound (intermolecular displacement) acts as a potential well to trap intramolecular excitations and prevent their dispersion. In the alpha-helix, amide-I groups are situated along the protein in three quasi one-dimensional molecular chains. In each of these chains, the adjoining peptide groups are held together by hydrogen bonds which link the amide-I nitrogen atom to the corresponding amide-I oxygen atom. Therefore, an intramolecular excitation on one N-C=O group will spread to its neighbors via dipole-dipole coupling and intermolecular displacements will be created against the hydrogen bonds N-C=O···H——N-C=O which join these groups together. These same hydrogen bonds are also responsible for creating and maintaining the spiral structure of the alpha-helix.[21]

*Solitons have found rather wide application in the physical and applied sciences. There are a number of general reviews[17,18] and specialized reports[19,20] available to the reader.

In 1979, numerical studies were carried out at the Los Alamos National Laboratory which confirmed the theoretical prediction that certain "threshold" conditions on the hydrogen bond nonlinearity must be satisfied for a Davydov soliton to be viable.[22] This suggestive finding motivated Scott[23] to improve and expand Davydov's original numerical model for the exciton-phonon coupled soliton. The modified version of Davydov's equations included ten additional dipole-dipole coupling terms between adjacent amide-I groups in the alpha-helix. The primary aim was to decide whether it would be reasonable to find solitons on typical alpha-helical proteins. Since ATP hydrolysis releases approximately 0.49 ev of free energy, it was assumed that two (0.206 ev) amide-I quanta launch the energy pulse on two adjacent spines of an alpha-helix. For the hydrolysis of one ATP molecule,* the numerical computations on the modified Davydov model demonstrated soliton organization at a critical level of hydrogen bond nonlinearity which is equal to that obtained from self-consistent field calculations on the formamide dimer. Also these calculations showed that the internal dynamics of the soliton are governed primarily by two frequencies. This observation predicted a laser-Raman spectrum which is in close agreement to the Raman spectrum of metabolically active Escherichia coli, as measured by Webb.[24] Organisms that are not metabolically active do not demonstrate such Raman active modes, so induction of resonances by laser light is not responsible for the observations. Only cells metabolizing glucose demonstrated the wave numbers shown below. Based on a soliton "interspine oscillation" with a period of 2×10^{-12} seconds (spectral energy, $E_1 = 17\ cm^{-1}$) and a second "longitudinal speed" component of the soliton with a period of $8/3 \times 10^{-13}$ seconds (spectral energy, $E_2 = 125\ cm^{-1}$) a spectrum can be constructed, by $E_2 \pm E_1$, for the internal dynamics of a soliton which is very similar to Webb's measurement of metabolically active Escherichia coli.[25,26] This laser-Raman data provides encouraging experimental evidence to suggest that Davydov solitons play a functional role in the metabolic process. In addition, from recent solid state experiments with acetanalide, there is further substantive evidence to suggest that solitons exist in hydrogen bonded chains of amide-I groups.[27]

For the purposes of this article, it is helpful to consider the Hamiltonian's which correspond to a soliton on a quasi one-dimensional molecular chain:

$$\hat{H}_{soliton} = \hat{H}_{exciton} + \hat{H}_{phonon} + \hat{H}_{interaction} \qquad (1)$$

*See the article by A. C. Scott in these proceedings for a proposed mechanism of resonant energy coupling between ATP hydrolysis and the C=O stretch.

where,

$$\hat{H}_{exciton} = \sum_n E_o \hat{B}_n^+ \hat{B}_n - J(\hat{B}_{n+1}^+ \hat{B}_n - \hat{B}_{n-1}^+ \hat{B}_n) \quad (2)$$

$$\hat{H}_{phonon} = \frac{1}{2} \sum_n [\frac{1}{M} \hat{P}_n^2 + w(\hat{U}_n - \hat{U}_{n-1})^2] \quad (3)$$

$$\hat{H}_{interaction} = \chi \sum_n (\hat{U}_{n+1} - \hat{U}_{n-1}) \hat{B}_n^+ \hat{B}_n \quad . \quad (4)$$

Equation (2) is the Hamiltonian which corresponds to intramolecular excitations on the one-dimensional chain and is indexed by position n along the chain. For an alpha-helix, this excitation is essentially the C=O stretch (amide-I, Eo = 0.206 ev or ~ 1660 cm^{-1}) in a quasi linear chain of ···N-C=O···N-C=O··· groups. The C=O stretch is treated in quantum mechanical terms and accordingly, $\hat{B}n^+$ and $\hat{B}n$ are creation - annihilation operators for this mode. The J term is the resonance interaction energy for adjacent N-C=O dipoles and by definition it is a dispersive term that couples amide-I groups to their nearest neighbors along the chain. Equation (3) is the Hamiltonian which corresponds to intermolecular displacements within the N-C=O···H——N-C=O chain. In contrast to the quantum mechanical nature of (2), this sound energy equation is classical and includes both kinetic and potential energy statements. M is displaced mass along the chain and $\hat{P}n$ is the momentum operator canonically conjugate to the one-dimensional displacement $\hat{U}n$ within the chain. The w parameter is the linear restoring force per unit change in hydrogen bond length. Finally, Eq. (4) is the Hamiltonian which corresponds to intramolecular and intermolecular coupling within the chain. It relates displacement between neighbors $(\hat{U}n+1 - \hat{U}n-1)$ to the probability amplitude $\hat{B}n^+ \hat{B}n$ of the C=O stretch. Particular emphasis should be placed on the χ term, since this constant orders the degree of nonlinear coupling between exciton and phonon fields. In relation to the alpha-helix, this coupling constant represents the degree of nonlinear interaction by the hydrogen bond and it must be above a critical threshold for soliton formation to occur. In other words, nonlinear coupling between intramolecular excitations and intermolecular displacements minimizes dispersion; it is the "glue" which holds a soliton together.

The next section on general anesthesia will explain how anesthetic molecules are capable of altering the J, w and χ terms in the Hamiltonian equations. However, before proceeding with this section it is helpful to introduce the continuum approximation equations for a soliton and to derive the nonlinear Schrödinger equation. Davydov[4] assigns the soliton wave function as

$$|\psi \text{ soliton} > = \sum_n a_n(t) e^{\theta(t)} \hat{B}_n^+ |0> \quad (5)$$

which is normalized to unity by

$$\sum_n |a_n|^2 = 1 \ . \tag{6}$$

The above wave function contains the operator

$$\hat{\sigma}(t) \equiv - \frac{i}{\hbar}\sum_n [\beta_n(t)\hat{P}_n - \pi_n(t)\hat{U}_n]$$

From this it follows that the average values of the displacement and momentum operators are

$$\beta_n(t) = \langle \psi sol \,|\hat{U}_n|\psi sol\rangle \tag{8}$$

and

$$\pi_n(t) = \langle \psi sol|\hat{P}_n|\psi sol\rangle \ . \tag{9}$$

The unknown functions $a_n(t)$, $\beta_n(t)$ and $\pi_n(t)$ are found by minimizing

$$\{a_n, \beta_n, \pi_n\} \equiv \langle \psi sol|\hat{H}sol|\psi sol\rangle \ . \tag{10}$$

By introducing the dimensionless variable ξ, a change to the continuum approximation is accomplished by introducing the functions $a(\xi,t)$, $\beta(\xi,t)$ and $\pi(\xi,t)$ such that $a(n,t) = a_n(t)$, $\beta(n,t) = \beta_n(t)$ and $\pi(n,t) = \pi_n(t)$. The minimum condition for (10) corresponds to the following set of differential equations:

$$[i\hbar \frac{\partial}{\partial t} - \Lambda + J \frac{\partial^2}{\partial \xi^2} - 2\chi \frac{\partial \beta(\xi,t)}{\partial \xi}] \ a(\xi,t) = 0 \tag{11}$$

$$[\frac{\partial^2}{\partial t^2} - V_{aq}^2 \frac{\partial^2}{\partial \xi^2}]\beta(\xi,t) - \frac{2\chi}{M} \frac{\partial}{\partial \xi} |a(\xi,t)|^2 = 0 \tag{12}$$

where

$$\Lambda = E_o + W - 2J \ , \qquad V_{aq}^2 = \frac{w}{M} \ \text{ and}$$

$$W = \frac{1}{2} \int \left[M(\frac{\partial \beta}{\partial t})^2 + w(\frac{\partial \beta}{\partial \xi})^2 \right] d\xi. \tag{13}$$

Since a Davydov soliton moves slowly with respect to the sound speed, the first term in Eq. (12) can be neglected. After removal and differentation once with respect to ξ, Eq. (12) reduces to:

$$\frac{\partial \beta(\xi,t)}{\partial \xi} = - \frac{2\chi}{MV_{aq}^2} |a(\xi,t)|^2 \ . \tag{14}$$

Placing Eq. (14) into (11) and replacing V_{aq}^2 with w/M gives

$$i\hbar \frac{\partial a(\xi,t)}{\partial t} - \Lambda a(\xi,t) + J \frac{\partial^2 a(\xi,t)}{\partial \xi^2} + \frac{4\chi^2}{\omega} |a(\xi,t)|^2 a(\xi,t) = 0. \qquad (15)$$

By introducing the new coordinate "A" such that $a(\xi,t) = A(\xi,t)$ $\exp -i/\hbar\Lambda t$ and shifting to subscripts to denote partial differentiation, a familar form of the nonlinear Schrödinger equation emerges which is phase shifted with respect to (15):

$$i\hbar A_t + JA_{\xi\xi} + 4\frac{\chi^2}{\omega} |A|^2 A = 0 \ . \qquad (16)$$

Finally, changing to a new time derivative by denoting $\tau = Jt$ and $G_o = 4\ \chi^2/J\omega$ gives

$$i\hbar A_\tau + A_{\xi\xi} + G_o |A|^2 A = 0 \ . \qquad (17)$$

With relation to the nonlinear Schrödinger equation, it is valuable to note that there are two ways to understand and model the disturbance of solitons. The first method involves changing the shape of the soliton's envelope, which is affected by a change in the value of the nonlinear term $Go|A|^2A$. If G_o is allowed to vary as a function of ξ, such that $G(\xi) = G_o + \varepsilon G_1(\xi)$ and $\varepsilon>0$, then the height and width of the soliton will vary as a function of the dimensionless coordinate ξ. Generally, relatively smooth and continuous variations in the value of $G(\xi)$ allow a soliton to adjust its height and width to the changing nonlinearity and to propagate with mild disturbance. However, relatively abrupt and discontinuous variations in the value of $G(\xi)$ do not allow enough time for a soliton to adjust itself as it propagates through the changing nonlinearity. In instances of abrupt change, the shape and speed of the soliton may be altered and usually such interactions are accompanied by an increased radiation of energy from the soliton. In studying abrupt variations, the ratio $G(\xi)/G_o$ and the width of $G(\xi)$ in relation to the width of the soliton are important considerations. These relations are also important when studying the disturbance of solitons by anesthetic agents. The second method of disturbance involves a loss of energy from the soliton by means of frictional or damping forces. This problem has been studied analytically by Davydov and Eremko,[28] with the finding that these forces tend to slow the propagation of the soliton and cause the pulse to grow a characteristic tail. For frictional forces proportional to soliton speed, they found the soliton's velocity decreased exponentially and for frictional forces proportional to the square of soliton speed, they found the soliton's velocity decreased nearly linearly with respect to time. The H-N-C=O moiety in an anesthetic molecule can be seen as a disturbance which damps energy from the soliton in the one-dimensional chain. However, this damping effect will be more related to the anesthetic's proximity to the chain rather than to the velocity of the soliton. In real physical systems, such as an alpha-helix, both of the disturbances that are

mentioned above are simultaneously at work. These disturbances may be inherent to the system, such as an alteration of true helical symmetry or the interaction of a side chain with the helix, or they may come from an extrinsic group that modifies the system.

The numerical results for an undistrubed Davydov soliton and for two distrubed solitons are shown below. For this study, the method of allowing the $\chi^2/J\omega$ term to change with translation along the helix is used in conjunction with a relative smooth and continuous variation in G and in conjunction with an abrupt variation in G. For a typical soliton having a half width of four helical turns the value G=1.1 is maintained, which is the condition that was studied by Scott.[23] For the perturbed cases, the value of G is increased to a maximum of 2.2. This increase in the value of G is purely phenomenological but, nevertheless, this number was chosen as a reasonable estimate of a physically relevant perturbation for the alpha-helix. An explanation for this change is given in the next section. A variation in G over twice a soliton's width (Fig. 3) was chosen to approximate minor translational changes in structure along the length of an intact alpha-helix and a narrower variation (Fig. 4) was chosen to approximate a more abrupt change in structure, such as those of an anesthetic interaction. The numerical method used in this study is essentially identical to that of Scott.[23] The numerical code simulates a longer (cytoskeletal type) alpha-helix which consists of 3 coupled chains of 200 H-N-C=O groups and in real terms this means that the molecule is 900 Å long, since each unit cell is 4.5 Å in length. A nonlinear coupling constant $\chi_1 = 0.40 \times 10^{-10}$ newtons was assigned to every hydrogen bond in the molecule, except where perturbations were introduced. This coupling constant is just above threshold for soliton formation, when two quanta of amide-I energy are used to initiate the pulse. For the three cases, the soliton was launched by placing a total of two quanta on spines 1 and 2 at H-N-C=O group = 1. At computer time T=0, all other H-N-C=O groups were at rest. In the area of perturbation, where G goes from 1.1 to 2.2, the minimum values of $X_1 = 0.30 \times 10^{-10}$ newtons, $\omega = 8.8$ newtons/meter and $J = 4.85$ cm^{-1} (or 0.09 computer units) were used. For the unperturbed spines $\omega = 19.5$ newtons/meter, $J = 7.8$ cm^{-1} (or 0.145 computer units) and the mass of a unit cell M = 114.2 x mass of a proton. Computer time (T) = $(M/\omega)^{\frac{1}{2}}$ = 0.90×10^{-13} seconds and sound speed = 4.5 Å $(\omega/M)^{\frac{1}{2}} = 4.56 \times 10^{13}$ Å/second. The time it takes a soliton to pass through one unit cell is 0.372 computer time units (T). This implies a soliton velocity of 1.65×10^{13} Å/second and a ratio of soliton to sound velocity of 0.37.

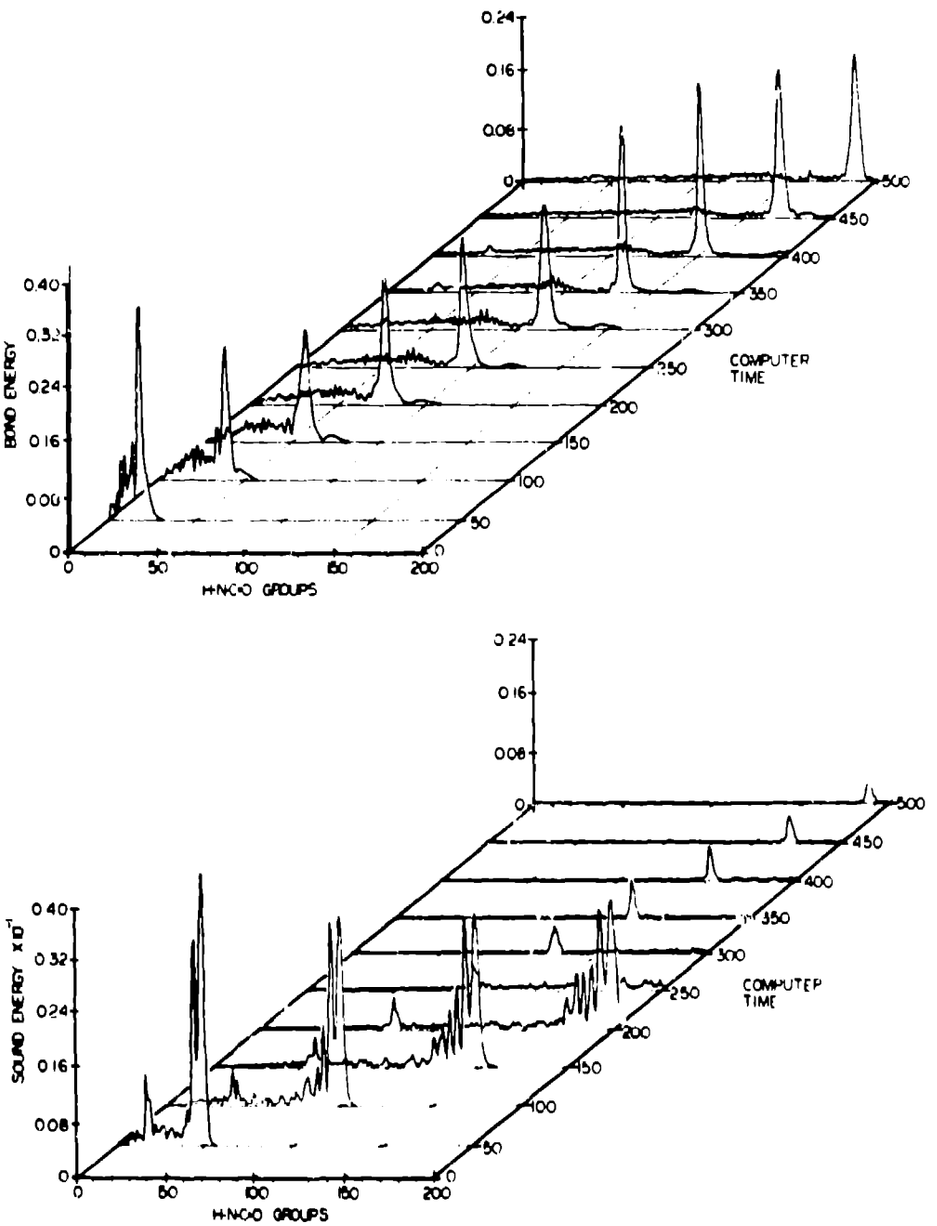

Fig. 2. Unperturbed soliton. When a soliton is initiated at one end of a helix, a typical amount of sound energy is not captured by the pulse. This energy moves at the sound speed and exits the helix by T = 225. The soliton consists primarily of bond energy (C=O stretch) and the total energy that is carried as sound energy is ~ 0.04%. The energy scales correspond to the summed energy on all three spines.

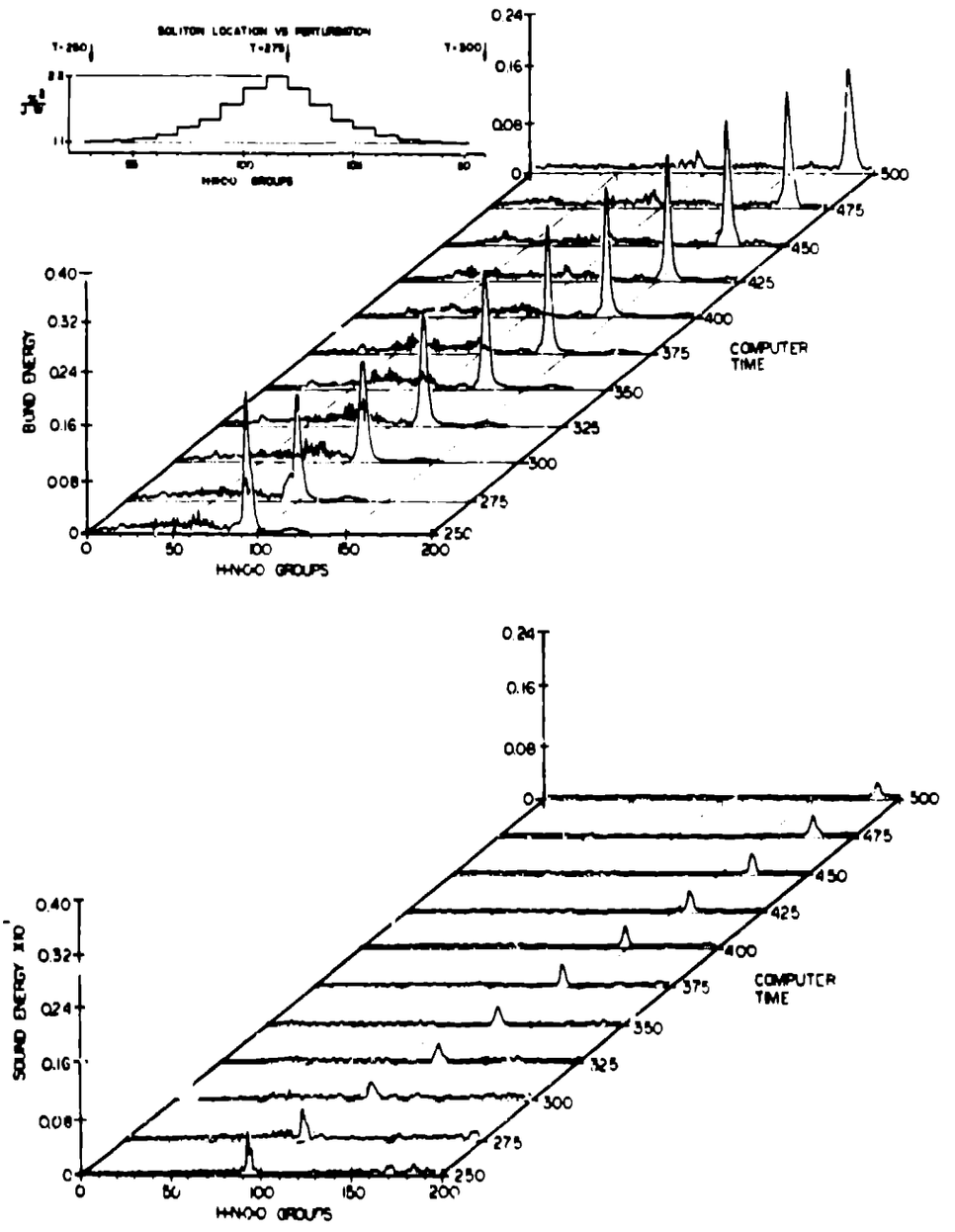

Fig. 3. Gradual disturbance. The changing value of G is shown by the upper insert. At T = 500 the height of the soliton is ~ 80% of the unperturbed pulse and the width is ~ 10% broader. Minimal energy is radiated by the soliton at the point of maximum perturbation T = 275. This ramp-like disturbance allows the soliton to adjust itself as it moves through the changing values of G. Up to T = 250 soliton propagation is identical to Fig. 2.

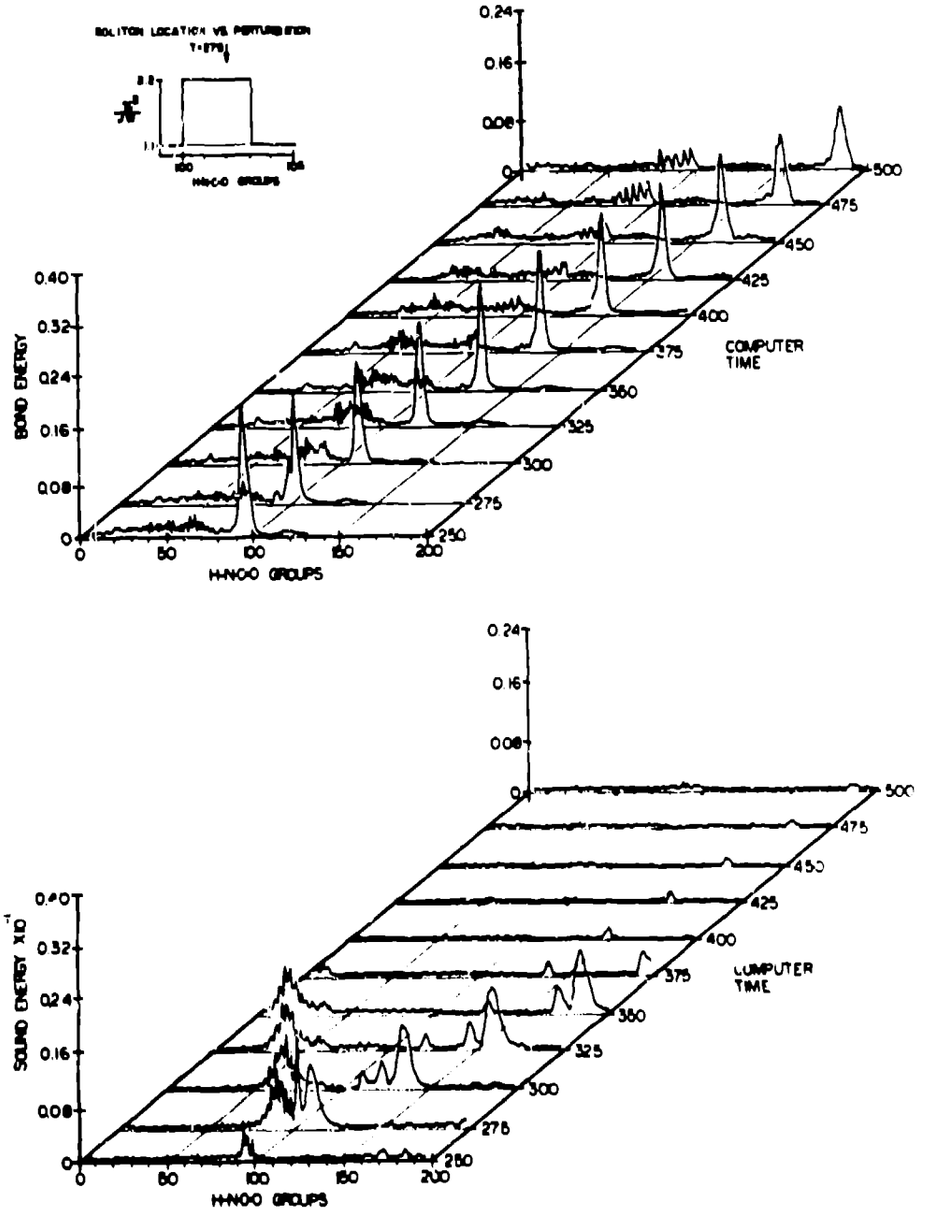

Fig. 4. Abrupt disturbance. The wall-like change in G is shown by the upper insert. At T = 500 the height of the soliton is ~ 50% of the unperturbed pulse and the width is ~ 20% broader. Also a tail has been formed which trails energy behind the soliton. At T = 275, increased sound energy is radiated by the soliton as it cuts through the region of perturbation. This abrupt disturbance does not allow the soliton to adjust itself as it moves through the changing value of G. Up to T = 250 propagation is identical to Fig. 2.

THE H-N-C=O GROUP: A COMMON DENOMINATOR OF INHIBITORY ACTIVITY

In order for a soliton to travel through an alpha-helix, several basic requirements must be satisfied: 1. The amide-I spines, which consist of three separate chans of repeating H-N-C=O groups, must be sufficiently one-dimensional to propagate the longitudinal sound and bond energy of a soliton. These chains spiral through a 3.61 amino acid per turn alpha-helix with a rotational translation of ~ 30° per H-N-C=O group. 2. The nonlinear hydrogen bond coupling between adjacent amide-I groups must be above threshold for retroactive interactions to take hold. 3. The vibrational energy must be sufficiently robust for this retoractive coupling to take hold. Since barbiturates contain four H-N-C=O groups in a rigid planar structure, it is straightforward to see that this anesthetic molecule is a congregated amide-I dipole which can hydrogen bond to an alpha-helix. Therefore, an interaction of a barbiturate with an alpha-helix might alter profoundly either the propagation or the formation of solitons at the location where the anesthetic molecule associates with the protein.

The hydrogen bonding of a barbiturate to an alpha-helix will distort and break the intermolecular hydrogen bonds that are responsible for creating and maintaining the spiral structure of the protein. This hydrogen bonding may occur via a simple two-point association, as shown in Fig. 1, or it may involve a more complex geometry between anesthetic and protein molecules. For example, many helical membrane proteins are known to be combinations of both parallel and antiparallel alpha-helices and the cytochrome proteins are a good example of this configurational motif. Commonly four alpha-helices, which are ~ 40Å long and separated by ~ 5Å, line up together to create a larger up-and-down helix bundle.[29] It is likely, for a more complex anesthetic-protein interaction, that a barbiturate will occupy a variety of inter- and intramolecular positions within the tightly packed cytochrome protein. These various positions may involve the breaking of hydrogen bonds within the H-N-C=O chains of the cytochrome or they may involve interactions within the side chains of the helices that help to stabilize the overall up-and-down structure of the protein. Fortunately, in spite of the enormous variety of interactions between anesthetic and protein molecules, the disturbance of energy migration may still be understood in terms of the three Hamiltonians for the Davydov soliton.

First, the "J" term in the exciton Hamiltonian (Eq. 2) can be altered by the association of an anesthetic molecule with a helix. This term gives the resonance interaction energy between adjacent amide-I dipoles and is approximated by the standard formula for two parallel dipoles

$$J = \frac{\vec{d}^2}{4\pi\varepsilon_o R^3}\,(3\cos^2\theta - 1) \qquad (18)$$

where $\vec{d}$ is the dipole moment, R is the distance between dipoles, ε_o is the dielectric coefficient and θ is the angle between dipoles. Since an anesthetic molecule may break the hydrogen bonds in an alpha-helix and cuase it to unwind, the distance R between neighboring dipoles will increase. This increased distance can appreciably affect the interaction energy because $J \propto 1/R^3$. More complete dynamical models for solitons on the alpha-helix include additional dipole-dipole coupling terms between neighbors.[23] These additional dipole coupling terms will also be shifted by the distorsion in helical shape but the major effects should occur at the point of anesthetic binding. Furthermore, the four amide-I moties that are inherent to the barbiturate ring are also capable of dipole coupling to the alpha-helix. Such a coupling will depend on the relative angles between the anesthetic and protein H-N-C=O groups and in most instances this coupling will act to damp energy from a soliton. In the numerical study of the previous section, only the J term was changed as a phenomenological estimate of an anesthetic interaction. It was decreased from 7.8 cm^{-1} to 4.85 cm^{-1}, which corresponds roughly to an increased distance R from 4.5 Å to 5.3 Å. From consistent force field calculations on the hydrogen bond,[30] an increase in hydrogen bond length of ΔR = 0.8 Å corresponds approximately to a drop in hydrogen bond energy of 55%. This empirical decrease in the J term was chosen as a hopefully conservative estimate of an anesthetic interaction with a protein, since the hydrogen bond remains intact at this level of distorsion. More complete estimates should include changes in all dipole-dipole coupling terms and damping due to the presence of anesthetic amide-I.

Second, both the "M" and "ω" terms in the phonon Hamiltonian (Eq. 3) can be altered by the association of an anesthetic molecule with a helix. Since a barbiturate molecule may dipole couple and bind to the spines of an alpha-helix, it may act to increase the dynamic mass M of a soliton. This amount of increased mass may help to reduce the propagation velocity of the soliton and lengthen the perturbation time for the anesthetic molecule. This effect was not included in the numerical study, as it was not considered to be of primary importance. The spring constant ω for the hydrogen bond is related to the energy of the bond which, in turn, is dependent to the length and angle of the bond. Longer and less energetic hydrogen bonds in proteins demonstrate lower force constants which are associated with higher N-H and C=O stretching forces. This means that upon hydrogen bonding -N-H → O=C-, the energy of N-H and C=O stretching declines.[31] The spring constant ω can also be considerably affected by change in the N-H$\angle$O=C angle,[30] since the strength of the hydrogen is rather sensitive to deviations beyond 20-30°. Therefore, it should be clear that an anesthetic interaction which unwinds and lengthens a hydrogen bond will diminish the spring constant for that bond. The extent to which this occurs, in relation to the change in hydrogen bond energy, is difficult to estimate accurately by simple methods. However, as a first approximation, the numerical study assumed a simple linear relationship between hydrogen

bond energy and the spring constant ω. Hence, at ΔR = 0.8 Å the restoring force ω = (19.5)(0.45) = 8.8 newtons/meter. This is a moderate estimate for a change in ω, since a completely broken hydrogen bond will have no intermolecular spring constant.

Third, the "χ" term in the interaction Hamiltonian (Eq. 4) can be changed by the association of an anesthetic molecule with a helix. It is well known that the C=O stretching mode occurs above 1700 cm^{-1} for a free carbonyl and that it is red shifted by hydrogen bonding.[32] Careri[33] points out that this red shift to ~ 1665 cm^{-1} is strictly proportional to the chemical shift of the proton as measured by NMR and this shift can be used as a good measure of hydrogen bonding. In line with this understanding, the exciton-phonon coupling constant χ is seen to be the shift in energy of an amide-I vibrational quantum per unit change in hydrogen bond length

$$\chi = \frac{dE_o}{dR} \qquad (19)$$

where Eo is the energy of an amide-I vibration and R is the length of the associated hydrogen bond. Scott[34] points out that $E_o \propto W^{\frac{1}{2}}$, where W is the spring constant of the C=O vibration, which allows (19) to be written as

$$\chi = \frac{E_o}{2W}\frac{dW}{dR} \qquad (20)$$

When an anesthetic molecule binds to a helix and causes it to unravel, the influence of a weaker hydrogen bond on dW/dR will decrease. This will affect a decline in the value of χ and blue shift the associated C=O stretch in the protein. Kuprievich and Kudritskaya[35] have calculated a value of $\chi = 3\text{-}5\times10^{-11}$ newtons and for the purposes of the present numerical study χ is taken at this lower limit to approximate the coupling constant for a weaker hydrogen bond. According to the findings of the numerical code, this value of χ is just below threshold for soliton formation when two quanta of amide-I energy initiate the pulse.

As a class of agent, barbiturates demonstrate a broad range of lipid solubility. For example, thiopental has one of the highest oil-water partition coefficients at 4.7, whereas barbital has one of the lowest at 0.21. Factors that elevate the partition coefficient include both increased molecular weight (by C5 substitution) and decreased ionization at physiologic pH. It is well known that increased lipid solubility is associated with a shortened onset of action, a shortened duration of action, an enhanced hypnotic potency and an enhanced interaction with hydrophobic regions of protein.[36] Especially important to the hypothesis of membrane activity is this last property of increased hydrophobic interactions with proteins. It should be clear that barbiturates are capable of binding to both plasma and membrane proteins because as much as 70% of plasma concentrations are bound to albumen during general anesthesia. Hence, factors which increase lipid solubility will also increase anesthetic-protein interactions at the neuronal and mitochondrial lipid mimbranes.

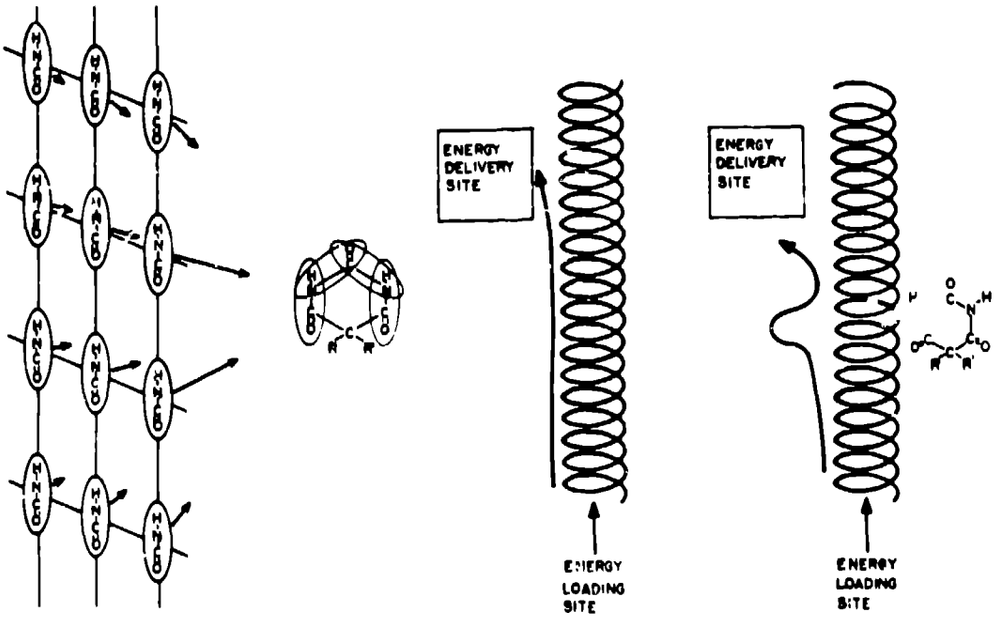

Fig. 5. (a) The interaction of barbiturate's four H-N-C=O dipoles with the dipoles of an alpha-helix. The protein is represented by a two-dimensional projection and the arrows indicate the relative energy of resonant interaction which is proportional to $1/R^3$ and dependent upon the angle between dipoles. (b) The propagation of a soliton can be disturbed by a barbiturate molecule. Thus when a soliton is launched, it does not make it to its energy delivery site.

To induce general anesthesia, the concentration of barbiturate in whole brain tissue must be on the order of 200 micromolar.[37] Since most anesthetically useful barbiturates demonstrate a lipid to water partition coefficient of ~ 4:1 and since whole brain tissue consists of cytosol greater than lipid, it is reasonable to calculate a membrane concentration of 200 x 4 = 800 micromolar during general anesthesia. This concentration is equivalent to a volume distribution of ~ 2×10^6 $Å^3$/barbiturate. Taking cytochrome C' as an average membrane protein,[29] which as mentioned earlier consists of four 40 Å helices separated by ~ 5 Å, implies a protein which encompasses a volume of about 20 Å x 20 Å x 40 Å = 1.6×10^4 $Å^3$/molecule. Therefore, during general anesthesia approximately $1.6 \times 10^4 / 2 \times 10^6 \times 100 = 0.8\%$ of typical membrane proteins are associated with an anesthetic molecule. This rough calculation assumes a uniform volume distribution and no increased affinity of hydrogen bonding anesthetics for proteins. Nonetheless, this 0.8% figure appears rather large, especially when one considers that fewer than ten prostaglandin molecules can alter the behavior of an entire cellular membrane. This

figure also suggests a cooperative association among membrane proteins, since a possible inhibition of ~ 1% of membrane activities results in a 10-15% decrement in CNS oxygen consumption.

In addition to barbiturates, there are a number of classes of hypnotic and antiepileptic agents that have a similar H-N-C=O containing structure. From Fig. 6, it noted that hydanotoins contain three, succinimides and glutethimides contain two, and urethanes contain one functional amide-I moiety. Hydantoins, succinimides and trimethadione are commonly used antiepileptic agents, whereas glutethimides are used as human and urethanes are used as veterinary hypnotics. When trimethadione is N-methylated, it is inactive until the hepatic microsomal enzymes demethylates the parent compound to the active N-H structure. Such structure-activity relationships support the proposal that the entire H-N-C=O moiety is required for soliton perturbing functions. Also the number of amide-I moieties in these agents appears to be related to potency. In conjunction with this, molecular conformational energy calculations have confirmed that the one-point hydrogen bonding abilities of barbiturates, hydantoins and succinimides is unrelated to either their hypnotic or antiepileptic activities. Further, these studies have suggested that hypnotic and antiepileptic agents require the participation of more than one carbonyl or amide hydrogen for the production of pharmacologic activity.[38,39] This suggestion of complete H-N-C=O participation supports the soliton model of anesthetic activity.

The soliton model of general anesthesia also presents an attractive mechanism of action for GABA. Much as with barbiturates, GABA is capable of assuming a two-point hydrogen bonding interaction with the amide-I spines of an alpha-helix. However, unlike barbiturates GABA is not a stiff planar ring nor does it contain a strict H-N-C=O group. Hence, its four carbon backbone would be capable of mutual resonance with the lower frequencies of a Davydov soliton and can be viewed as a resistor which acts in parallel with the amide-I spine. Raman spectroscopy has demonstrated that GABA in aqueous solutions has an intramolecular hydrogen bonded skeletal vibration at 90 cm^{-1}. This has led Nielsen[40] to propose that GABA resonantly couples and damps vibrations in biological molecules. Curiously, the internal frequencies of a soliton are nearly resonant with this GABA mode.[26] However, for completeness it should also be pointed out that alpha-helical poly- (L-alanine) demonstrates a Raman spectrum at similar low frequency wave numbers[31] which have been accounted for by linear molecular dynamic calculations on the alpha-helix.[41,42] Therefore, an important question is whether GABA damps the linear thermal modes or the nonlinear nonthermal modes of a soliton in proteins. A number of publications have pointed out that barbiturates potentiate the inhibitory action of GABA in neurons.[43,44] These publications have also gone on to suggest that GABA and barbiturates act on the same "receptor site" but they have failed to specify its molecular configuration. Since both GABA and the planar

H-N-C=O ring component of barbiturates are not optically active, it is reasonable to propose that one of their sites of action is across the one-dimensional spine system of an alpha-helix. Gamma-aminobutyric acid is understood to be a major inhibitory neurotransmitter in the central nervous system. The assignment of GABA as a neurotransmitter which resonantly damps protein activities is consistent with its inhibitory role.

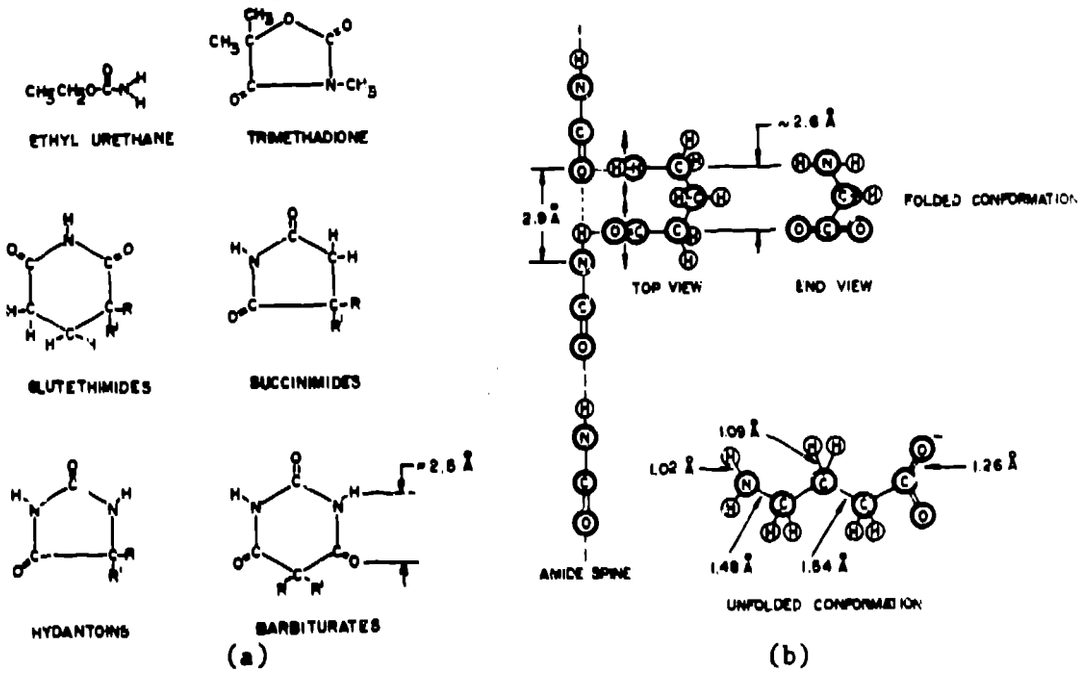

Fig. 6. (a) Anesthetic and antiepileptic agents that are capable of disturbing solitons. The presence of an alkyl or aryl group at R and R' confers increasing lipid solubility and, generally, increased lipid solubility promotes an increased drug potency. (b) Intramolecular hydrogen bonded conformation of gamma-aminobutyric acid which is capable of interacting with the alpha-helix. The mode shown in the top view occurs at 90 cm^{-1} which is nearly resonant to the calculated internal frequencies of a soliton.

In summary, up to the present there has not been a satisfactory model to account for barbiturate's diverse activities. Theories have implicated barbiturate's hydrogen bonding ability as a mode of action but they have failed to provide a specific context for activity. The soliton model offers a unifying mechanism of action for a number of diverse agents, such as, barbiturates, hydantoins, glutethimides, succinimides and urethanes. It accounts for the observation that barbiturates (and antiepileptic agents) appear to enhance GABA's inhibitory activity. It accounts for the observation that barbiturates display no stereospecific activity at anesthetic concentrations

since the one-dimensional spine system of an alpha-helix cannot be stereospecific. It accounts for the observation that N-methylated derivatives of barbituric acid are "ultrashort" hypnotics, since N-methylation will "choke" the total number of H-N-C=O configurations in the anesthetic ring. Finally, it relates the number of H-N-C=O groups in the molecule to hypnotic potency.

GLYCOPROTEINS IN RELATION TO THE AMIDE-I RESONANCE

Central to Davydov's idea is that the amide-I resonance acts as a basket for the storage and transport of biological energy. In its original context, this idea was applied only to the alpha-helical protein. However, the article by P. S. Lomdahl in these proceedings points out that Davydov's theory may be expanded to a more generalized protein structure. In instances of translational variance in structure, the dispersion of amide-I energy may hold a key for understanding protein dynamics. It is in this vein that the role of sialic acid (or N-acetyl sugars) in glycoproteins on the cellular surface will be discussed. Curiously, sialic acid contains an H-N-C=O group at its C2 position and, therefore, the glycoprotein may be seen as a macromolecule of unusual flexibility with respect to the amide-I.

The vast majority of glyoproteins in cells, ~ 70% for neurons, are located on the membrane surface which makes up only ~ 5% of the total cellular volume.[45] This large reservoir of glycoproteins literally covers the membrane surface and lends it a negative charge by right of its ionized polysaccharide component. The numerous roles of glyoproteins on the cellular surface are only partially understood but despite this it is known that they are implicated in cellular adhesion, cellular migration, cellular identity, intracellular communication, memory consolidation and transmembrane signaling.[46] It is fair to say that glycoproteins are "workingmen" of the cellular membrane. They are in close association with the intracellular machinery and the filamentous cytoskeleton which just subjacent to the membrane surface. Therefore, as Adey emphasizes, they play an important and seminal role in transductive coupling.[47] Edelman has pioneered much of the work in this area with his theory of glycoprotein modulation[48] and it is along this line that Davydov's idea on the amide-I might also be useful. Basically, Edelman's idea is that the behavior of glycoproteins can be modulated by changing their sialic acid (or amide-I) content. This change in sialic acid somehow alters the manner in which the glycoprotein operates on the cellular surface and it also purportedly changes the manner in which the polysaccharide component of a glycoprotein relates to its protein component. Since a glycoprotein is essentially a two-component macromolecule (protein and polysaccharide) the key to understanding this modulating behavior might come from looking at the specific changes in the polysaccharide fraction.

Glycoproteins are oriented in the lipid bilayer such that the polysaccharide rich portion of the macromolecule is located primarily on the outer membrane.[49] At this extracellular location, the sugar fraction of the glycoprotein consists of both straight and branched chain polysaccharides which are covalently bound to the peptide backbone. Thus the polysaccharide portion of the macromolecule forms a "cloud" of sugar molecules around the protein core and this tethered cloud carries a fixed negative charge by right of its ionized polysaccharide component. Katchalsky[50] has pointed out that these negative charges are neutralized by binding cations, particularly divalent cations, in a long-range cooperative manner with the following affinities: $H^+ = K^+ > Na^+$ and $Ca^{2+} > Mg^{2+}$. The anionic polysaccharide cloud around the core protein expands and contracts under the influence of cations and in general, the divalent cations $Ca^{2+} > Mg^{2+}$ cause contraction (or gelling) while the monovalent cations $H^+ = K^+ > Na^+$ all promote expansion.[51,52] Katchalsky has likened this behavior to that of an "isothermal macromolecular machine" because he notes that such contraction and expansion movements within glycoproteins are capable of performing work.

In central nervous system tissue, three covalent carbohydrate-protein linkages are associated with glycoproteins. About 90% of these covalent linkages are associated with asparagine-N-acetylglucosamine, while the remaining 10% of covalent linkages are associated with either serine or threonine residues.[53,54] It has been shown conclusively that molecules of N-acetylglucosamine and N-acetylgalactosamine (sialic acid) are concentrated nearer the core of the glycoprotein rather than on the periphery of the macromolecule.[55,56] This means that the amide-I groups of sialic acid are closely associated with the amide-I groups in the core protein. In addition, the primary attachment residue asparagine is classified as a neutral amino acid. This means that the side chain may be found both inside and outside the core protein. Generally, the side chains of neutral polar residues are found outside the molecules although they can reside inside the core protein if their polar groups are "neutralized" by hydrogen bonding to other like residues or to the carboxyl on the main chain.[57]

It should be apparent that glycoproteins have two methods at their disposal for changing their amide-I content and for changing the location of these amide-I groups in their polysaccharide fraction. Both of these methods are closely interrelated. By modulating their sialic acid content which is Edelman's idea, the manner in which energy disperses through the glycoproteins' structure can change. A variable number of amide-I groups in the polysaccharide fraction could significantly alter the nearby energy transport paths in the core protein. In other words, this loss of sialic acid could appreciably change the shape of the sialic acid-protein interaction which, in turn, could conceivably alter the amide-I dipole-dipole couplings within the glycoprotein. By changing the degree of polysac-

charide ionization or by changing the cation concentration in the solvent, which is Katchalsky's isothermal machine idea, the paths through which amide-I energy disperses might again change. Differing concentrations of cations, especially Ca^{2+}, would place the H-N-C=O groups of sialic acid and the asparagine side arms in varying juxtapositions with respect to the amide-I groups in the core protein. This action would alter the shape of the sialic acid-protein interaction which again could alter the dipole-dipole couplings within the glycoprotein. As in the first mechanism, this could change the paths through which glycoproteins disperse amide-I energy.

Since a substantial number of membrane proteins are in the helical configuration[58] and since many of these membrane proteins are also glycoproteins, it is reasonable to suggest that a some fraction of glycoproteins contain helical protein cores which traverse the

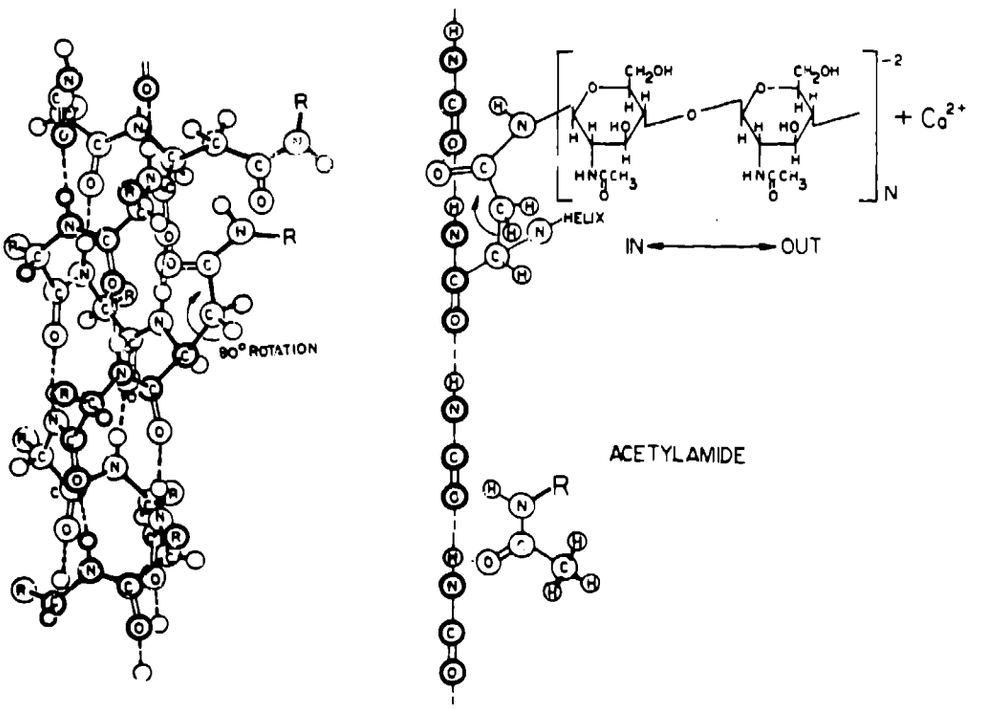

Fig. 7. (a) Asparagine's side chain contains an amide-I group. This amino acid accounts for 90% of the covalent carbohydrate-protein linkages in glycoproteins. (b) Amide-I spine system of an alpha-helix in relation to asparagine-N-acetylglucosamine-β-1-4-N-acetylglucosamine which initiates a clear majority of covalent carbohydrate-protein linkages in glycoproteins. The amide-I resonance is inherent to all N-acetyl sugars at the core of glycoproteins. The location of these H-N-C=O groups depends sensitively on both Ca^{2+} concentration and sialic acid content.

lipid bilayer. In relation to such a glycoprotein, I would like to suggest that the soliton could be a useful device for transmembrane coupling. Since there is no ATP outside the cellular membrane to excite the amide-I resonance, it may be assumed that a soliton would be initiated by the hydrolysis of ATP just subjacent to the membrane. When the soliton reached the other side of the membrane it would interact with the polysaccharide portion of the glycoprotein which is replete with sialic acid. These sugars, which contain the amide-I resonance, could interact with the outgoing soliton and create a variety of behaviors: absorb the pulse, reflect the pulse, or absorb and reflect varying amounts of the pulse. This interaction would depend on the number and location of sialic acid molecules which, in turn, would depend on glycoprotein "modulation" and on cationic concentrations. Since glycoproteins act as receptors for hormones, neurotransmitters and intercellular contacts, it is possible that the binding of these ligands to their receptors would alter the positions of sialic acid groups which, in turn, could modify energy propagation at the membrane surface. In other words, the glycoprotein may be a transductive device that allows the inner membrane to perform "spectroscopy" on the outer membrane.

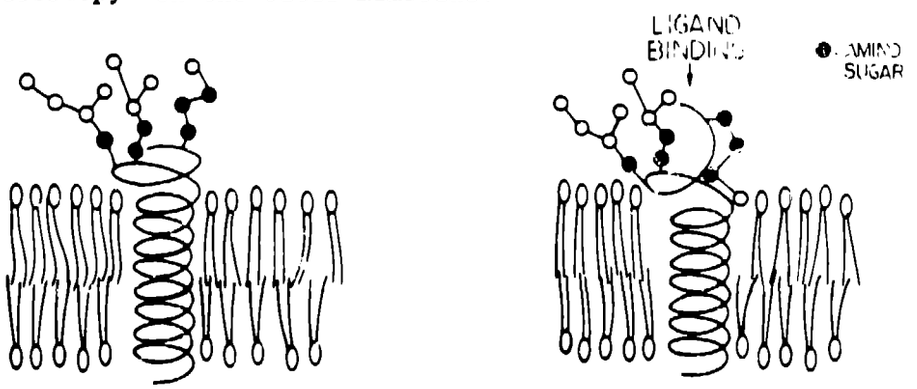

Fig. 8. The binding of a hormone or transmitter substance to its respective glycoprotein changes the relative positions of the sialic acid (or amino sugar) molecules. This alters the amide-I dipole-dipole coupling relations in the glycoprotein. The propagation of a soliton may, thereby, be subject to a variety of changes when it reaches the membrane surface. Circles indicate sugars and the coil indicates an alpha-helix in the lipid bilayer.

ACKNOWLEDGMENT

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NUMERICAL METHODS

Details of the numerical computations are nearly identical to those given in references 22 and 23 except for the following points: The calculations were integrated using a leapfrog predictor-corrector method. For computations where there were changes in χ, J and ω values a time step was chosen to minimize the relative error per unit time interval. The accuracy of the time integration was checked by rerunning the calculations with a smaller time step and rerunning the calculations with a third order predictor second order corrector method with an equivalent time step. No significant differences were found between the smaller time steps and the two methods of integration.

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